PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 September 1997 (05.09.97)	
International application No. PCT/EP97/00627	**Applicant's or agent's file reference** P-313
International filing date (day/month/year) 12 February 1997 (12.02.97)	**Priority date** (day/month/year) 14 February 1996 (14.02.96)
Applicant DE FLORA, Silvio et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   04 August 1997 (04.08.97)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Jocelyne Rey-Millet

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
ZAMBON GROUP S.P.A.
Corporate Patent & Trademark Dept.
Attn. Panossian, Stefano
via Lillo del Duca, 10
I-20091 Bresso (Milan)
ITALY

Applicant's or agent's file reference p313	Date of mailing *(day/month/year)* 03/07/1997 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 97/00627	International filing date *(day/month/year)* 12/02/1997
Applicant ZAMBON GROUP S.P.A. et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Monika Schmitz

Form PCT/ISA/220 (January 1994)

09/125022
403 Rec'd PCT/PTO 10 AUG 1998

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
p313		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 97/ 00627	12/02/1997	14/02/1996
International Patent Classification (IPC) or national classification and IPC		
A61K31/71		
Applicant		
ZAMBON GROUP S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/08/1997	
Name and mailing address of th IPEA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P.J.L. 02551 Telephone No.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP97/00627

I. Basis of th r port

1. This report has been drawn up on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*

☒ the international application as originally filed

☐ the description, pages , as originally filed
pages , filed with the demand
pages , filed with the letter of

☐ the claims, Nos. , as originally filed
Nos. , as amended under Article 19
Nos. , filed with the demand
Nos. , filed with the letter of

☐ the drawings, sheets / fig. , as originally filed
sheets / fig. , filed with the demand
sheets / fig. , filed with the letter of

2. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.

☐ the drawings, sheets / fig.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 (c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Claims		YES
	Claims	1-12	NO
Inventive Step	Claims		YES
	Claims	1-12	NO
Industrial Applicability	Claims	1-12 (see below)	YES
	Claims		NO

2. Citations and Explanations

Reference is made to the following documents:

D1: US-A-4331648
D2: J. Clin. Invest., Vol.68, 1981, pages 1053-1064; J.H. Doroshow et al.
D3: Seminars in Oncology, Vol.10(1), 1983, pages 29-34; R.D. Olson et al.
D4: Toxicology and Applied Pharmacology, Vol.54, 1980, pages 168-175; R.W. Freeman et al.
D5: US-A-4873088
D6: Seminars in Oncology, Vol10(1), 1983, pages 53-55; C. Myers et al.
D7: Cancer Research, Vol.50(7), 1990, pages 2018-2021; F. Imamura et al.
D8: Minnesota Medical Association, 1984, pages 333-335; D.T. Kiang et al.

1.Claims 1-12 involve compositions or substances in a method of treatment of the human/animal body.
For the assessment of the present claims 1-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.It is pointed out that the documents "International Journal of Cancer, Vol.67, September 1996, pages 842-848" and "Clinical & Experimental Metastasis, Vol.14, September 1996, page 24" could be relevant for novelty for the subject-matter of claims 1-12 if the priority of the

pending application, which has not been checked is considered as invalid.

3.1.Documents D1, D2, D3 and D4 disclose the treatment of tumours with a combination of N-acetyl-cysteine (NAC) and Doxorubicin (DOX). NAC is said to block DOX cardiotoxicity without interfering with the antitumoral activity of DOX. D4 (see page 174, right column) further suggests that the NAC-DOX combination potentiates the antineoplastic effect of Doxorubicin (named adriamycin in D4).
The doses used are within the ranges claimed by the present invention.
It is pointed out that the terms "composition" or "kit" in the sense of the present invention include also two separate pharmaceutical forms of the two drugs for concurrent administration.
Furthermore, the capacity to metastasize is a characteristic of all malignant tumours and an antitumoral drug or composition will necessarily inhibit cancer metastasis formation.
3.2.Regardless of the effect (protective or synergistic) exerted by NAC in the composition, D1 to D4 anticipate the novelty of the composition (or kit) containing NAC and DOX, of its preparation as a medicament and of its use in a method for inhibiting cancer metastasis. The discovery of the synergistic effect of NAC plus DOX in the inhibition of cancer metastasis formation can not confer novelty to a composition or kit containing NAC and DOX, to its preparation as a medicament and to its use in a method for inhibiting cancer metastasis.
Therefore, in view of D1 to D4 the subject-matter of claims 1-12 cannot be considered as being novel and does not meet the requirements of Article 33(2) PCT.

4.Moreover, Document D5 discloses compositions containing liposome-encapsulated DOX (adriamycin) in combination with a secondary compound, such as the adriamycin-protective compound NAC (see column 4, line 45 to column 5, line 3; column 8, lines 23-39; claim 11). This liposomal formulation of DOX can be used as antitumoral composition for treating metastatic diseases (see column 15, lines 6-57). DOX doses are between 20-100mg per dose.
Document D6 describes the combined treatment with DOX and NAC of patients with metastatic soft tissue sarcomas. The percentage of patients with stable disease plus those with partial remissions was 50% for DOX plus NAC (see page 54, right column).
D7 suggests that the treatment with DOX (adriamycin) that does not eliminate all tumour cells may increase the incidence of invasion and metastasis, although the number of total tumour cells would be decreased by the drug. NAC suppressed the DOX-induced potentiation of invasiveness. In order to avoid DOX unfavourable effect (and therefore to inhibit cancer metastasis formation related to exposure to DOX) without impairing its cytocidal activity, D7 recommends the use of a combination DOX-NAC for successful chemotherapy.
D8 describes the use of NAC for preventing the cardiotoxicity from DOX (adriamycin) in the treatment of metastatic breast cancer (see page 334).
Therefore, the lack of novelty in sense of Article 33(2) PCT is further emphasized by the

disclosure of documents D5 to D8 as follows (taking into account the remark made in point 3.2. above):
-lack of novelty of claims 1-3,5,7,9,10,12 with regard to D5
-lack of novelty of claims 1-12 with regard to D6
-lack of novelty of claims 1-3,10 with regard to D7 and D8

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1.The following printing errors have not been corrected:
-"sinergistically" (page 1, line 30; claim 2) should read "synergistically"
-"colture" (page 5, line 23; page 8, line 22) should read "culture"

2.Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D3 to D8 are not mentioned in the description, nor are these documents identified therein.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

I. Basis f the rep rt

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☐ the description, pages . as originally filed
pages . filed with the demand
pages , filed with the letter of

☐ the claims, Nos. . as originally filed
Nos. . as amended under Article 19
Nos. . filed with the demand
Nos. . filed with the letter of

☐ the drawings, sheets / fig. . as originally filed
sheets / fig. , filed with the demand
sheets / fig. . filed with the letter of

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☐ the claims, Nos.

☐ the drawings, sheets / fig.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 (c)).

4. Additional observations, if necessary:

V. **Reasoned statement under Article 35(2) with regard t n velty, inventive step or industrial applicability; citations and xplanations supporting such statement**

1. Statement

Novelty	Claims		YES
	Claims	1-12	NO
Inventive Step	Claims		YES
	Claims	1-12	NO
Industrial Applicability	Claims	1-12 (see below)	YES
	Claims		NO

2. Citations and Explanations

Reference is made to the following documents:

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2.It is pointed out that the documents "International Journal of Cancer, Vol.67, September 1996, pages 842-848" and "Clinical & Experimental Metastasis, Vol.14, September 1996, page 24" could be relevant for novelty for the subject-matter of claims 1-12 if the priority of the

pending application, which has not been checked is considered as invalid.

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It is pointed out that the terms "composition" or "kit" in the sense of the present invention include also two separate pharmaceutical forms of the two drugs for concurrent administration.
Furthermore, the capacity to metastasize is a characteristic of all malignant tumours and an antitumoral drug or composition will necessarily inhibit cancer metastasis formation.
3.2.Regardless of the effect (protective or synergistic) exerted by NAC in the composition, D1 to D4 anticipate the novelty of the composition (or kit) containing NAC and DOX, of its preparation as a medicament and of its use in a method for inhibiting cancer metastasis. The discovery of the synergistic effect of NAC plus DOX in the inhibition of cancer metastasis formation can not confer novelty to a composition or kit containing NAC and DOX, to its preparation as a medicament and to its use in a method for inhibiting cancer metastasis.
Therefore, in view of D1 to D4 the subject-matter of claims 1-12 cannot be considered as being novel and does not meet the requirements of Article 33(2) PCT.

4.Moreover, Document D5 discloses compositions containing liposome-encapsulated DOX (adriamycin) in combination with a secondary compound, such as the adriamycin-protective compound NAC (see column 4, line 45 to column 5, line 3; column 8, lines 23-39; claim 11). This liposomal formulation of DOX can be used as antitumoral composition for treating metastatic diseases (see column 15, lines 6-57). DOX doses are between 20-100mg per dose.
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D7 suggests that the treatment with DOX (adriamycin) that does not eliminate all tumour cells may increase the incidence of invasion and metastasis, although the number of total tumour cells would be decreased by the drug. NAC suppressed the DOX-induced potentiation of invasiveness. In order to avoid DOX unfavourable effect (and therefore to inhibit cancer metastasis formation related to exposure to DOX) without impairing its cytocidal activity, D7 recommends the use of a combination DOX-NAC for successful chemotherapy.
D8 describes the use of NAC for preventing the cardiotoxicity from DOX (adriamycin) in the treatment of metastatic breast cancer (see page 334).
Therefore, the lack of novelty in sense of Article 33(2) PCT is further emphasized by the

disclosure of documents D5 to D8 as follows (taking into account the remark made in point 3.2. above):
-lack of novelty of claims 1-3,5,7,9,10,12 with regard to D5
-lack of novelty of claims 1-12 with regard to D6
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The following defects in the form or contents of the international application have been noted:

1.The following printing errors have not been corrected:
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-"colture" (page 5, line 23; page 8, line 22) should read "culture"

2.Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D3 to D8 are not mentioned in the description, nor are these documents identified therein.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
p313		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 97/00627	12/02/1997	14/02/1996
Applicant		
ZAMBON GROUP S.P.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established by this Authority to read as follows:

   PHARMACEUTICAL COMPOSITION ENABLING TO INHIBIT CANCER METASTASIS FORMATION CONTAINING N-ACETYLCYSTEINE AND DOXORUBICIN

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/00627

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 10-12 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00627

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/71 //(A61K31/71,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	INTERNATIONAL JOURNAL OF CANCER, vol. 67, no. 6, 17 September 1996, pages 842-848, XP000675221 S. DE FLORA ET AL.: "SYNERGISM BETWEEN N-ACETYLCYSTEINE AND DOXORUBICIN IN THE PREVENTION OF TUMORIGENICITY AND METASTASIS" see the whole document ---	1-12
P,X	CLINICAL & EXPERIMENTAL METASTASIS, vol. 14, no. S1, September 1996, page 24 XP000675205 A. ALBINI ET AL.: "PREVENTION OF TUMORIGENICITY AND METASTASIS IN MURINE MODELS BY N-ACETYLCYSTEINE AND SYNERGISM WITH DOXORUBICIN" see the whole document --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
13 June 1997	03.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Hoff, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 331 648 A (JR. MYERS ET AL.) 25 May 1982 see the whole document	1-12
X	US 4 873 088 A (MAYHEW ET AL.) 10 October 1989 see abstract see column 4, line 45 - column 5, line 17 see column 8, line 23 - line 46 see column 15, line 6 - column 16, line 7; claims	1-3,5,7, 9,10,12
X	J. CLIN. INVEST., vol. 68, no. 4, 1981, pages 1053-1064, XP000067349 J.H. DOROSHOW ET AL.: "PREVENTION OF DOXORUBICIN CARDIAC TOXICITY IN THE MOUSE BY N-ACETYLCYSTEINE" cited in the application see the whole document	1-12
X	SEMINARS IN ONCOLOGY, vol. 10, no. 1, 1983, pages 53-55, XP000675353 C. MYERS ET AL.: "A RANDOMIZED CONTROLLED TRIAL ASSESSING THE PREVENTION OF DOXORUBICIN CARDIOMYOPATHY BY N-ACETYLCYSTEINE" see the whole document	1-12
X	SEMINARS IN ONCOLOGY, vol. 10, no. 1, 1983, pages 29-34, XP000675354 R.D. OLSON ET AL.: "INFLUENCE OF N-ACETYLCYSTEINE ON THE ANTITUMOR ACTIVITY OF DOXORUBICIN" see the whole document	1-12
X	TOXICOLOGY AND APPLIED PHARMACOLOGY, vol. 54, no. 1, 1980, pages 168-175, XP000675334 R.W. FREEMAN ET AL.: "EFFECT OF SULFHYDRYL-CONTAINING COMPOUNDS ON THE ANTITUMOR EFFECTS OF ADRIAMYCIN" see the whole document	1-12
X	CANCER RESEARCH, vol. 50, no. 7, 1990, pages 2018-2021, XP000675346 F. IMAMURA ET AL.: "POTENTIATION OF INVASIVE CAPACITY OF RAT ASCITES HEPATOMA CELLS BY ADRIAMYCIN" see the whole document	1-3,10

-/--

International Application No
PCT/EP 97/00627

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MINNESOTA MEDICAL ASSOCIATION, vol. 67, no. 6, 1984, pages 333-335, XP000675351 D.T. KIANG ET AL.: "BREAST CANCER TODAY" see page 334 ---	1-3,10
A	INTERNATIONAL JOURNAL OF CANCER, vol. 61, no. 1, 1995, pages 121-129, XP000675336 A. ALBINI ET AL.: "INHIBITION OF INVASION, GELATINASE ACTIVITY, TUMOR TAKE AND METASTASIS OF MALIGNANT CELLS BY N-ACETYLCYSTEINE" cited in the application see the whole document -----	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 97/00627

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4331648 A	25-05-82	NONE	
US 4873088 A	10-10-89	EP 0153955 A	11-09-85
		WO 8500968 A	14-03-85